Department of Genetics, University of Wisconsin
Madison, Dec. 26, 1951

Dear Cavalli:

I was very glad to hear from you, and to take this opportunity to exchange best wishes for the New Year. I wish I could report that much had happened since the Cold Spring Harbor meetings, but I have been almost immobilized with various distractions. I have the comfort of seeing progress in the laboratory in the hands of my wife and my students. The genetic behavior of lysogenic phage, on one hand, and of the entire heredity of Salmonella on the other are very perplexing. You will doubtless have been reading Evelyn Witkin's Microbial Genetics Bulletin, and will be au courant des affaires. Mrs. Lederberg and I have completed one task that was much more interesting in comcept tham in application. The replica-plating technique is mentioned in the last M.G.B., but in case you have not heard or remembered about it, it is a method to make several copies on different media of the growth on an initial plate. Velveteen fabric is used to make the precise transfer, much as in a hectograph printing process. Aside from the great convenience of replica plating for finding mutants and testing recombinants, the technique makes it possible to isolate pre-adapted mutants without direct selection. A smoothly grown plate (inoculated with 10^8-10^9) is replicated to selective agar (e.g., phage or streptomycin) plates. The resistant mutants occur in superimposable positions, correspponding to the clones on the original plate (and proving their occurrence). By taking inocula from the indicated sites on the original plate, the resistant mutants may be enriched by as much as 100-fold. Such inocula are replated at lower dilution and the process reiterated until the enrichment results in well-isolated colonies that give rise to pure cultures. The actual enrichment line is never exposed to the selective agent; in general the process is like pedigree selection of roosters or bulls for egg or milk prduction. A complete account will appear in the Jan. 1952 Jour. Bacteriology, but I give this hasty summary in anticipation you may have an immediate interest in the method. More recently, I have started some work with actinomycetes. Heterokaryosis probably occurs with moderate regularity in S. griseus; the evidence for recombination (stable prototrophs) is so far ambiguous, and I am just starting to look at some other "species".

I would welcome an opportunity to discuss your findings on the possibility of heterothallism in some detail. I do not reach the same conclusions from the data you given although I am also prejudiced by some of our own findings. You will agree that any pair of the following can be crossed: 58-161S^r; K-12; W-1177. In your material, it is the derived $T+L+B_1+$ that is unique, behaving differently from K-12, n'est-ce pas? Using this as an indicator, you then find that different $T-L-B_1-$ can be found (by recombination) which now can be crossed with the der.$T+L+B_1+$. I will admit that you have differential fertility, but I think it may be premature to call it heterothallism. Mrs. Lederberg asks me to mention that she accidentally picked up a B-M- strain which is now sterile with Y-10, W-677 etc. Like your stock, it can be crossed with re-derived TLB_1- (obtained by segregation from diploids). The picture is very similar: I think we can infer that your TLB_1+ strain suffered the same accident as our B-M- (some steps from 58-161). If, as I think likely, this strain would be useful to your further study of these relationships, and you are planning to continue this, she will be pleased to send it to you (if we can verify these old findings). Have you noticed that $T-L-B_1-$ isolated by crosses on TLB_1.sm agar show the linkage peculiarities like those of segregants from persistent diploids. (p.12 and table 5b, my CSH ms.) This was my conclusion in one experiment. From it, I have given up trying to map with these cultures (one student is trying to straighten out some of the anomalies), but we are slowly devloping new cultures, avoiding the use of artificial mutagens. I have the same trouble with B- in 58-161: have you tried to recover B- recombinants on biotin agar, where sparing by methionine would not interfere? Nothing new on cytology. Miss Lively is spending most of her time on single cell isolations (to get the true segregation ratios from diploids; cf. table 9 CSHms. I have heard a little from Hayes: from this, I would judge (possibly prematurely) that he is making unnecessarily complicated deductions.

We would like very much to visit Italy and yourself, even at a Congress. The problem is purely financial. Let us know just what we should send you, and we will try to do so by return mail.

Yours sincerely,
Joshua Lederberg
Joshua Lederberg

P.S. Have you heard of anything (locally) about flagellar phages (Sertic & Boulgakov)? I am very anxious to look at these. JL